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CLINICAL INVESTIGATION **Brain**

VALIDITY OF THE GRADED PROGNOSTIC ASSESSMENT–DERIVED INDEX TO PREDICT BRAIN-METASTATIC PATIENTS' SURVIVAL AFTER GAMMA KNIFE RADIOSURGERY

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Purpose: To appraise whether the graded prognostic assessment (GPA)–derived index is valid for selecting patients with brain metastases for Gamma Knife (GK) radiosurgery.
Methods and Materials: A total of 56 consecutive patients in recursive partioning analysis (RPA) Class I (*n* = 19, 34%) and II (*n* = 37, 66%) formed the basis of this retrospective study. Their mean age was of 57 years with mean Karnofsky performance score of 77. Primary cancers stemmed mainly from the lungs (59%). A total of 45 patients (80%) harbored multiple tumors. The mean clinical follow-up period was 9 months.
Results: Kaplan-Meier analysis demonstrated that the overall median survival time (MST) for the whole series was 11.5 months: 16.5 vs. 6.5 months for RPA class I and II (*p* = 0.017). Multivariate Cox analysis revealed that female patients and a pre-GK good functional state were favorable prognostic factors. The favorable MST was in patients with a GPA score of 3 to 4 (17 months) followed by a GPA score of 2 to 2.5 (11 months) and GPA score 0 to 1.5 (6.5 months), but without statistical differences (*p* = 0.413) in between. A modified index (MGPA) is proposed with gender as a cofactor, then there existed a distinct survival differences (*p* = 0.028) between patients with an MGPA score of 3.5 to 5 (15 months) and with an MGPA score of 0 to 3 (7 months). In addition, the original GPA index failed to imply the difference of MST in patients with lung origin.
Conclusions: The GPA-derived index is not applicable to our set of patients for comparing their survival after GK radiosurgery. The gender of the patients is a suggested cofactor to further refine the greater prognostic accuracy of the GPA index. © 2010 Elsevier Inc.

Brain metastasis, Grading system, Prognosis, Radiosurgery, Survival.

INTRODUCTION

Brain metastasis occurs in 20% to 40% of cancer patients (1), and its incidence will likely increase as imaging techniques improve and new systemic treatments become available for prolonging the lifespan of affected patients (2). This disease often leads patients to suffer from serious neurologic and cognitive deterioration and is a direct cause of death in one-third to one-half of affected patients. Its prognosis is poor and variable with an overall median survival time (MST) of only 1 month without treatment and approximately 4 months after whole-brain radiation therapy (WBRT) (1, 2). Several studies reported that radiosurgery alone or plus WBRT could prolong lifespan of patients to another 4 to 6 months (3, 4). However, these clinical studies vary in their eligibility criteria and stratification features of patients. Are the favorable results attributable to the therapy alone or also in part to patient selection?

Many potential prognostic factors for patient survival had been presented in retrospective studies, but heterogeneous and controversial opinions still remain (5). In 1979, the Radiation Therapy Oncology Group (RTOG) developed three prognostic classes using recursive partitioning analysis (RPA) in 1,200 WBRT patients with brain metastases from three completed randomized trials (6). (Table 1) This analysis was based on age, Karnofsky performance status (KPS), primary tumor status, and presence of extracranial system metastases. Its validity had further been proved through the patient's prognosis after open surgery (7) or radiosurgery (8, 9). Until now, RPA classes have been applied as the universal standard for patient selection, prognostic prediction, and historical comparison for brain metastasis therapy.

In 2008, Sperduto *et al.* (10) presented a new Graded Prognostic Assessment (GPA) scoring index using the RTOG database of 1,960 metastatic patients from five randomized

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Table 1. Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification (6)

Class	Age (y)	KPS	Primary tumor	Extracranial metastases
I	<65	≥70	Controlled	No
II	≥65	≥70	Uncontrolled or synchronous	Presence
III	—	<70	—	—

Abbreviation: KPS = Karnofsky Performance Status.

Table 2. Graded Prognostic Assessment (GPA) Scoring system (10)

Score	Age (y)	KPS	No. of brain lesions	Extracranial metastases
0	>60	<70	>3	Present
0.5	50–59	70–80	2–3	—
1	<50	90–100	1	None

Abbreviation: KPS = Karnofsky Performance Status.

WBRT trials. This index is the sum of scores (0, 0.5, and 1.0) based on age, KPS, numbers of brain lesions, and presence of extracranial system metastases, but it dismisses the role of primary disease control. (Table 2) The GPA ranges from 0 (worst condition) to 4 (best condition). It was emphasized by the authors as prognostic as the RPA classes, and was also concluded to be the least subjective, most quantitative, and easiest method to be used than those available previously (10).

The goal of this retrospective study was to reappraise whether this GPA-derived prognostic index is generally applicable or can be recommended for historical comparisons based on our patients outcomes within a 5-year period.

METHODS AND MATERIALS

Patient series

Between July 2003 and December 2008, 56 consecutive patients in RPA Class I (n = 19, 34%) or II (n = 37, 66%) were retrospectively reviewed. All patients had contrast enhancing mass lesions on their brain CT/MRI associated with their primary cancers. In addition, 8 patients had prior histological confirmation from either a stereotactic biopsy (n = 5) or craniotomy (n = 3). Their preoperative mean KPS was 77 (range, 70–90). There were 20 men and 36 women with a mean age of 57 years (range, 32–82 years) at time of radiosurgery. Ten patients (17.9%) had undergone WBRT before the radiosurgery, and 6 patients (10.7%) had requests for WBRT made by family members after radiosurgery. The WBRT regimen was 30 Gy in 10 fractions. Overall, 4 patients (7.1%) had pre- and post–Gamma Knife (GK) WBRT, and 42 patients (75%) had been treated by GK radiosurgery only.

The primary cancers consisted of the lung cancer in 33 patients (58.9%), breast in 9 (16.1%), gastrointestinal in 5 (8.9%), and 2 (3.6%) each for hepatoma and urinary tract cancers. Only 11 patients (19.6%) harbored a single tumor, and more than 10 masses were noted for 2 patients. In all, 226 various brain metastatic brain tumors were collected. Most tumors were found within the frontal lobes (n = 96, 42.5%), followed by cerebellar (n = 36, 15.9%), occipital (n = 30, 13.3%) and parietal (n = 22, 9.7%) hemispheres. (Table 3) There were 9.7% tumors (n = 22) located deeply in midbrain and brainstem. The mean volume of all lesions was 3 ml (95% confidence interval, 2.0–4.1) ml.

All patients gave written informed consent for radiosurgery and for ongoing follow-up evaluations. Patients were followed up within 2 weeks after radiosurgery and thereafter were scheduled for clinical interview and neuroradiological studies every 3 months. Patients were also examined if their condition had changed. New lesions were appropriately retreated with GK radiosurgery if the patient's condition allowed.

Radiosurgical technique

All patients underwent GK radiosurgery under local anesthesia. We performed high-resolution magnetic resonance imaging (MRI) to define the target volume in every 2-mm axial planes and used the GammaPlan (version 5.43) for treatment planning. The enhanced tumor margin served as the radiosurgical target. All patients completed their treatment smoothly in a single session without any acute safety-related errors or complications. The mean prescribed maximal central dose was of 31 Gy (95% CI, 30.6–31.8 Gy) and the margin dose was 16 Gy (95% CI, 15.8–16.4 Gy) mostly along the 50% isodose line. When necessary, we plugged in selected beam channels within each collimator to shift the peripheral dose (≤8 Gy) curves away from the optic nerve or chiasm.

Statistical methods

All statistical analyses were performed with SPSS version 14 (SPSS Inc., Chicago, IL). A value of $p < 0.05$ (two-tailed) was considered statistically significant. The reference point for tumor control and patient survival was the date of the GK treatment. Tumor control was defined as the absence of any significant enlargement of the solid component or new lesions on MR and/or computed tomography (CT) images. The mainly analyzed variables included gender, age, pretreatment KPS, primary (lung vs. nonlung) cancer, and number of brain lesions. The nonparametric Kaplan-Meier

Table 3. Demographic characteristics of patients in this series

Men:Women	20:36
Age (y) (range)	57 ± 1.6 (32 –82)
KPS (range)	77 ± 1.2 (70–90)
Primary cancers (n = 56)	
Lung	33 (58.9%)
Breast	9 (16.1%)
Gastrointestinal	5 (8.9%)
Hepatoma	2 (3.6%)
Renal	2 (3.6%)
Ovary	1 (1.8%)
Buccal carcinoma	1 (1.8%)
Nasopharyngeal carcinoma	1 (1.8%)
Skin cancer	1 (1.8%)
Unknown	1 (1.8%)
Anatomic locations of lesions (n = 226)	
Frontal lobes	96 (42.5%)
Occipital lobes	30 (13.3%)
Parietal lobes	22 (9.7%)
Temporal lobes	16 (7.1%)
Cerebellar hemispheres	36 (15.9%)
Midbrain and brainstem	22 (9.7%)
Others	4 (1.8%)

Data are mean ± standard error of the mean.

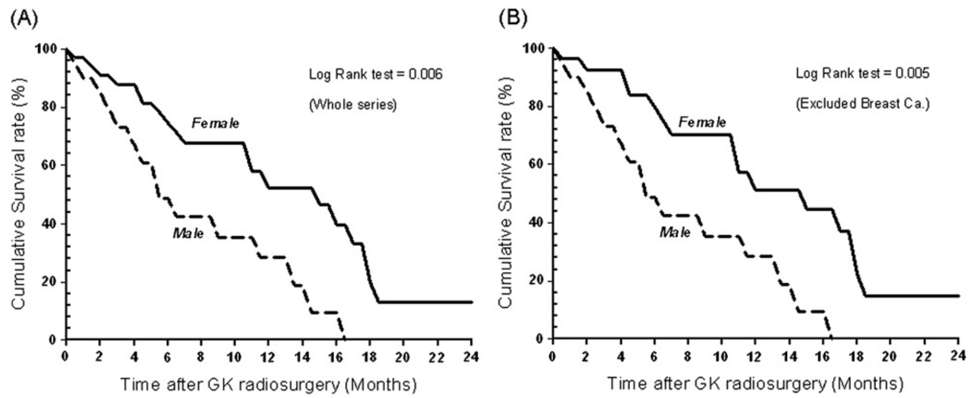

Fig. 1. Kaplan-Meier plot showing gender differences in the overall mean survival time of patients after Gamma Knife radiosurgery (a) in the whole series and (b) in the subgroup that excluded female patients with breast cancer.

method served to estimate the actual survival rates. The intergroups difference was calculated using the log-rank test. Data for patients alive at the time of last follow-up were treated as censored data (n = **22**, 39.3%, median follow-up 7.3 months). Variables that showed significant values were further re-entered for multivariate Cox proportional hazard regression model to analyze the hazard ratio (HR) of the potential prognostic indices for patient survival. Grouping of GPA scoring was stratified into two or three levels at different sums of scores. If the case numbers of individual subgroup was less than 10 patients, regroupings of multiple consecutive levels with similar outcomes were explored.

RESULTS

The mean and median clinical follow-up period of all patients was 9 and 6.5 months. Four patients (7.1%) underwent an open craniotomy approximately 6 months after the initial treatment because of an enlarged mass, and 11 patients (19.6%) underwent a second-time GK radiosurgery in a median period of 6 months (range, 2–9 months) because of some new growths outside the original locations. None of the other patients had any radiosurgery-related adverse sequelae. The overall local tumor control rate was 78.5%, and 34 patients (61%) had died of their primary cancers by the end of study. The Kaplan-Meier analysis revealed that the 6-months and 1-year survival rates of patients were 65.4% and 43.1%, respectively. Statistically, the overall MST for the whole series was 11.5 months. The WBRT at pre- or post-GK did not appear to have any influence on a patient's survival period.

Longer survival was noted in female patients (15 vs. 5.5 months, $p = 0.006$, Fig. 1a) or younger patients ($\leq$60 years, 13.5 vs. 6.5 months, $p = 0.45$), in patients of higher performance score (KPS >70, 15 vs. 6 months, $p = 0.033$), and in patients with lung cancer origin (12 vs. 9 months, $p = 0.93$). There were no differences in MTS stratified by tumor numbers. Generally, breast cancer would have a more indolent course than most of the other tumors, so 9 female patients of breast origin were excluded and reanalyzed to avoid the possibility of a confounding bias resulting from tumor histology differences. Similarly, a shorter MST was found in male patients (Fig. 1b) or patients with poor performance score (KPS = 70, $p = 0.029$) with a distinct statistical difference. Multivariate Cox analysis of whole series also revealed that male sex (HR = 2.47, 95% CI, 1.18–5.17, $p = 0.016$) and lower functional score (KPS $\leq$70; HR, 2.19; 95% CI, 1.01–4.76, $p = 0.049$) could be associated with a shorter life survival, independent of tumor histology.

Based on the RPA classification, the best survivors (Class 1) achieved an MST of 16.5 months in comparison to Class II patients, who achieved only 6.5 months ($p = 0.017$) (Fig. 2) The frequency distribution of GPA scoring for our patient population is shown in Fig. 3a. According to different cutoff points in every interval of 0.5 (*e.g.* 0.5, 1, 1.5 to 3.5) of the GPA scores, patients were stratified initially into dichotomous groups, but no statistically significant survival difference was observed among these groups. It was also impossible to define the four subgroups because of the few (<10) patients on both ends. By three-group stratification, the only one meaningful combination was as plotted in Fig. 4: GPA score, 3 to 4 (MST, 17 months); GPA score, 2 to 2.5 (MST, 11 months); and GPA score, 0 to 1.5 (MST, 6.5 months). However, there still were no statistically significant survival differences ($p = 0.413$) in between. This is

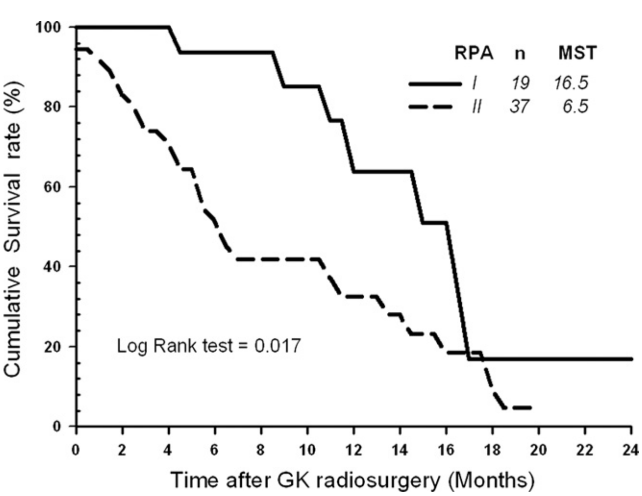

Fig. 2. Kaplan-Meier plot showing the overall mean survival time of patients after Gamma Knife radiosurgery based on recursive partitioning analysis (RPA) classes. A highly statistically significant difference ($p = 0.017$) between groups was observed.

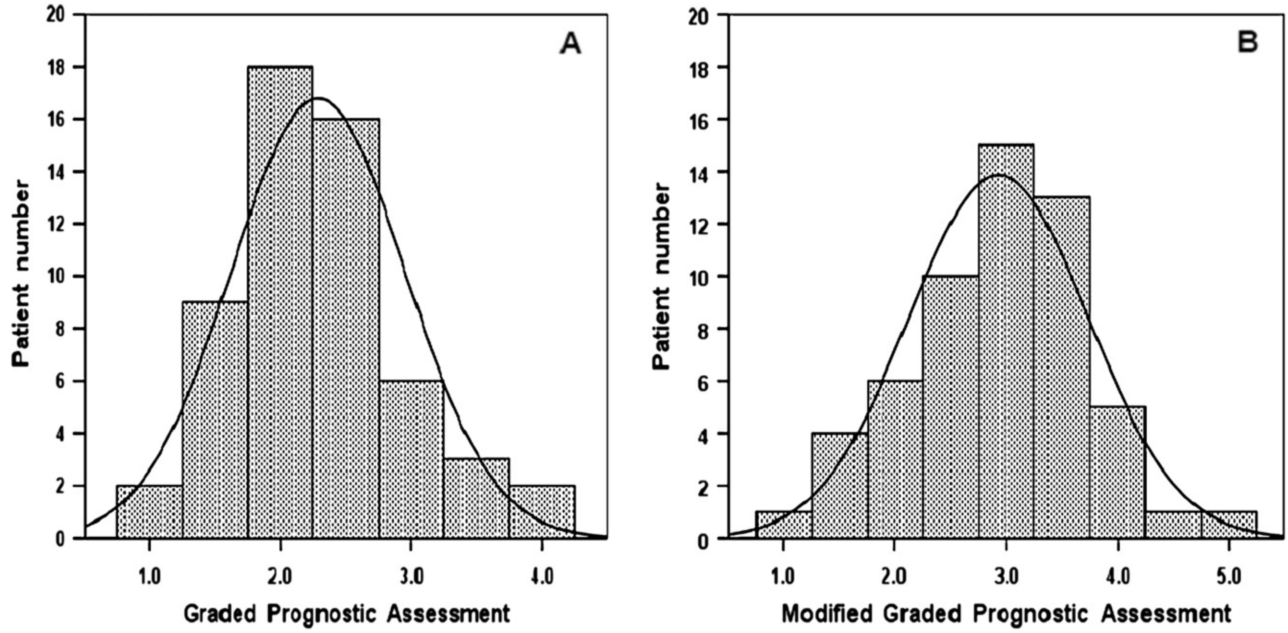

Fig. 3. Frequency distribution of the patients according to the original Graded Prognostic Assessment (GPA) (a) and the modified GPA index (b).

probably a result of both the limitations of the present study, with small numbers of patients, and/or an inherent limitation of the GPA analysis.

However, the important purposes of prognostic indices are to guide the choice of treatment for patients and to compare the therapeutic results in relatively homogeneous patient groups. Thus a good, valid predictive score could direct a tailored treatment for individuals, as the RPA class does, and should not be limited by patient numbers.

Based on previously mentioned analysis of our series, the author tried to modify the original GPA scoring plus the gender as a cofactor (Table 4, Fig. 3b). This modified GPA-derived index display a range of patients from 0 (worst condition) to 5 (best condition). Using the same principles of collapsed categories, the patients with the best survival has a MGPA score of 3.5 to 5 months (15 months), whereas the worst group (MGPA score, 0–3) achieved 7 months' median survival ($p = 0.028$). (Fig. 5). These results are similar to those based on the RPA index. Obviously, the original GPA system might leave out some insidious prognostic parameters.

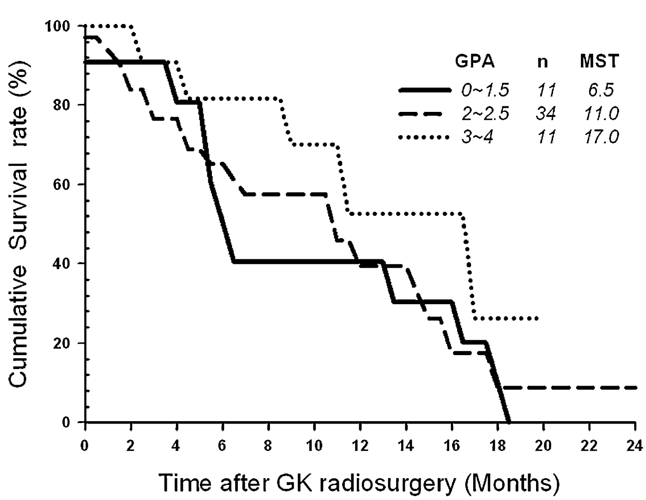

Fig. 4. Kaplan-Meier plot showing differences in overall mean survival time of patients after Gamma Knife radiosurgery based on the original Graded Prognostic Assessment (GPA) scoring index. No statistically significant difference between the subgroups was observed.

The survival rates with these three different indices are further reanalyzed in patients with cancer of lung origin ($n = 33$) or with multiple metastasis ($n = 45$) to make the comparison simpler (Table 5). Similarly, it is also impossible to classify patients into four subgroups as in the original GPA index. The 6- and 12-month survival rates are obviously similar for the worse prognostic groups in all three indices, whereas the 6-month survival rate is much better in the RPA index. Furthermore, both the RPA and MGPA index could distinguish patients with lung origin more clearly according to two classes. The median survival of patients based on the MGPA score (6.5 vs. 12 months) is more realistic than that based on the original GPA score (12 vs. 15 months) and is similar to that based on the RPA index (7 vs. 16.5 months).

DISCUSSION

Brain metastasis is biologically infiltrative in character (11), so complete resection is always impossible. Moreover, as in this series, nearly 80% of all patients harbor multiple brain tumors at the time of diagnosis, and approximately 10% to 15% of brain tumors are deep-seated (1). These patients are often in poor functional states and are not candidates for craniotomy. At present, surgery plus WBRT, WBRT or stereotactic radiosurgery alone, or the combination

Table 4. Modified Graded Prognostic Assessment (MGPA) Scoring system

Score	Age (y)	Sex	KPS	No. of brain lesions	Extracranial metastases
0	>60	Male	<70	>3	Present
0.5	50–59	—	70–80	2–3	—
1	<50	Female	90–100	1	None

Abbreviation: KPS = Karnofsky Performance Status.

of radiosurgery plus WBRT have been suggested to be helpful for prolonging patient's survival (1, 2). However, there still exists debate regarding the efficacy, within these retrospective clinical studies, of various features of patients that make them eligible for these treatment approaches.

It will be difficult to compare these competing therapeutic modalities unless there is a relevant, uniform prognostic index. Prognostic indices always combine two or more items of patient data such as age or sex to guide physicians in understanding the natural history of a disease, making a difficult clinical decision regarding a sound therapy plan, comparing the clinical outcomes to identify subsets of patients with poor outcomes, and planning follow-up strategies, as well as to promoting future research regarding potential treatments.

In 1999, Lagerwaard *et al.* (5) retrospectively reviewed many potential prognostic factors in 1,292 metastatic patients treated in a single institution. The investigators concluded that pretreatment KPS score, response to steroid treatment, systemic tumor activity, and serum lactate dehydrogenase had independent and strongest impacts on a patient's survival, second only to treatment modality. However, there still remained heterogeneous and controversial opinions regarding age, sex, site of primary tumor, and number of brain metastases. In our series, both univariate and multivariate Cox analysis demonstrated that male patients and patients with poor functional score (KPS, 70) had poor survival outcomes after radiosurgery ($p < 0.05$). More recently, Golden *et al.* (12) demonstrated that prognostic factors for the overall survival of metastatic cancer patients treated with radiosurgery varies by primary tumor site; but this viewpoint was not proved in present study with an analysis excluding female patients with breast cancer origin.

Over the past 20 years, many different prognostic systems have been developed. Among them, three systems (RPA, SIR, and BSBM) have been frequently used to guide the decision making for therapy as well as for comparison of clinical outcomes (6, 8, 9). Good performance status and control of the primary cancers are the only two universal factors for longer survival in these three indices; but the role of lesion numbers, volumes and location (at eloquent brain or not) did not provide enough evidence to reach an agreement.

Obviously, the prognostic index is complex and variable, according to our expectation. First, not all of the clinically relevant patient data are definitely reliable and optimally weighted, as previously mentioned, to be included in the model (13). Second, it is always impossible, as shown in

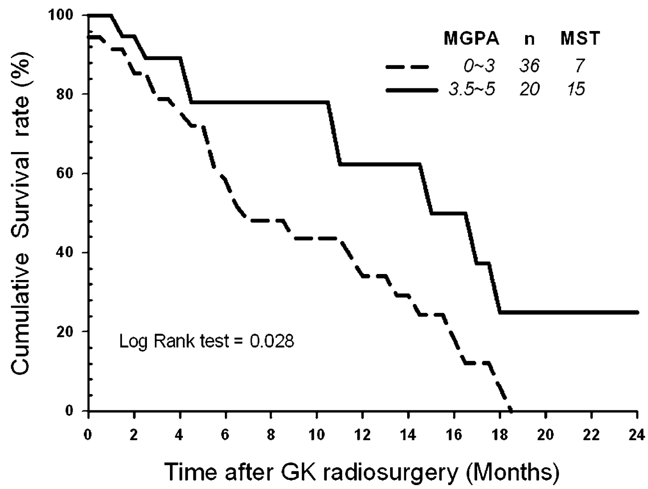

Fig. 5. Kaplan-Meier plot showing the difference in the overall mean survival time of patients after Gamma Knife radiosurgery based on the modified Graded Prognostic Assessment (GPA) scoring index. A statistically significant difference ($p = 0.028$) was observed between groups.

this study, to group patients simply by the relevant scales, and it is often necessary to stratify patients into several subgroups using the principle of collapsed categories (8, 9, 13). Thus there exists the definite possibility of arbitrarily defining the cutoff points for continuous variables (13) in different series, or the inability to avoid contamination by confounding factors (12). It can be argued that most published studies lack clinical credibility and evidence because they were reported based on relatively inhomogeneous patient groups (8, 9, 13). Furthermore, these scoring models (8–10) are not convenient and require data entry into a computer for making complex calculations (13). Most important, no single system works well for all individuals within a population. The prognostic usefulness of a system may be limited to only some specific primary tumor sites (12).

According to the original RPA index, the Class III patients had the shortest MST of 2.3 months after WBRT (6), so only those patients in the RPA Class I or II were included in the present analysis. In addition, a prognostic model is unlikely to be useful unless its predictions are accurate enough as well and its false negative/positive rate is low (13), so we endeavor to keep the case number of individual subgroup to at least 10 patients in this study. Comparable to previous reports (8–10, 12), our results confirmed the validity of the RPA index ($p = 0.017$) for historical comparisons of clinical outcomes, whereas the analysis of GPA index failed to retain statistical significance correlated with our patients' prognosis by two to four levels stratification, or even confined only to those patients with lung cancer origin.

Generally there is therapeutic agreement, concerning brain metastasis, that improvement of quality of life (*i.e.,* by preventing deterioration of neurologic and neurocognitive function) is more important than prolonging survival in these patients (1, 2). However, the optimal control of the primary cancer and systemic disease could not only improve quality

Table 5. Comparison of survival results with different prognostic indices in patients with lung origin ($n = 33$) or with multiple metastasis ($n = 45$) treated with Gamma Knife radiosurgery

	RPA I	RPA II	GPA 0–2	GPA 2.5 – 4	MGPA 0–2.5	MGPA 3–5<
Patients with lung origin ($n = 33$)						
No. of patients	10	23	17	14	13	20
Median survival (mo)	16.5	7.0	12	15	6.5	12
p Value	0.133		0.167		0.087	
6-Month survival	100 %	58.1 %	62.0 %	81.8 %	50.3 %	82.6 %
12-Month survival	80 %	34.6 %	42.3 %	54.5 %	42.0 %	47.7 %
Patients with multiple metastases ($n = 45$)						
No. of patients	16	29	27	18	20	25
Median survival (mo)	16.5	6	6.5	17	6.5	15
p Value	0.025		0.098		0.132	
6-Month survival	92.3 %	47.9 %	55.2 %	78.1 %	51.9 %	71.8 %
12-Month survival	68.4 %	39.2 %	40.9 %	67.0 %	38.9 %	55.4 %

Abbreviations: GPA = Graded Prognostic Assessment; MGPA = Modified Graded Prognostic Assessment; RPA = recursive partitioning analysis.

of life for the participating patients but could also be a dominant factor in prolonging a patient's lifespan (8, 9).

The main difference between the RTOG-RPA and GPA index system is that the GPA index incorporates the number of tumors as a factor but excludes the estimation of primary tumor control. The reason for this is that the later parameter is fraught with inconsistency in regard to the type and timing of imaging studies, which are difficult to be quantified and/or are subjective (10). In addition, the RPA class includes only three scales, so it can be concisely applied, whereas the GPA scoring index requires complex computation and always stratifies patients into several subgroups depending on the numbers within the whole series.

Although the status of primary cancer control is closely related to the performance score, presented already in both the RPA and GPA systems, its role related to patient survival should be heavily weighed rather than of overlooked for purposes of simplicity or convenience. The present study, just with the addition of the gender parameter, could make the original GPA-derived index more accurate in predicting and comparing prognosis of the patients, even limited to those patients with lung cancer origin or with multiple metastases. The author strongly suggests that the GPA system must lack some insidious prognostic parameters to be exposed. This newly proposed MGPA-derived index should be further validated by using larger, prospective, multi-institutional, randomized patient populations with brain metastases who have undergone or not undergone stereotactic radiosurgery.

CONCLUSION

In conclusion, this 5-year follow-up retrospective study at a single institution confirmed the validity of the RTOG-RPA index for comparing survival of patients with brain metastases. However, the original GPA-derived prognostic scoring system is not applicable to our patient population and has yielded some different results. The main obstacle is the uncertainty and difficulty of stratifying patients. Moreover, the present study revealed that the gender factor could be added to achieve better accuracy. The author strongly suggests that there might be some insidious prognostic parameters to be included in the original GPA index.

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